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Synthesis, Chiral Resolution, and Absolute Configuration of Dissymmetric 4,15-Difunctionalized [2.2]Paracyclophanes

Georg Meyer-Eppler,[†] Rebecca Sure,[‡] Andreas Schneider,[†] Gregor Schnakenburg,[§] Stefan Grimme,[‡] and Arne Lützen*,[†]

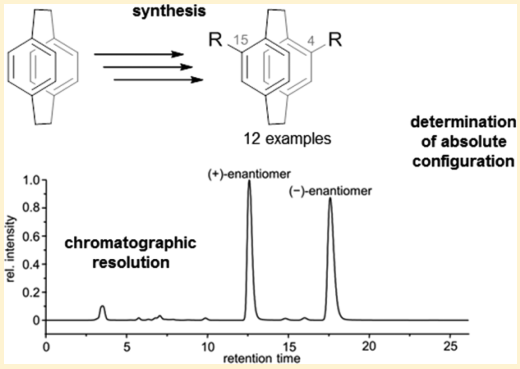
[†]Kekulé-Institute of Organic Chemistry and Biochemistry, University of Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany

[‡]Mulliken Center for Theoretical Chemistry, University of Bonn, Beringstr. 4, D-53115 Bonn, Germany

[§]Institute of Inorganic Chemistry, University of Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany

Supporting Information

ABSTRACT: Despite the fact that functionalized planar chiral [2.2]-paracyclophanes have received a lot of attention, the chemistry of pseudo-*meta* 4,15-distubstituted [2.2]paracyclophanes is largely unexplored. This is mainly due to the fact that the 4,5-dibromo-functionalized [2.2]-paracyclophane is much less prone to halogen-metal exchange reactions than its constitutional pseudo-*ortho* or pseudo-*para* isomers. Here, we give an account of an efficient protocol to achieve this, which allows the synthesis of a broad variety of 4,15-disubstituted [2.2]paracyclophanes. Furthermore, we were able to resolve several of the racemic compounds via chiral HPLC and assign the absolute configurations of the isolated enantiomers by X-ray diffraction and/or by the comparison of calculated and measured CD-spectra.



INTRODUCTION

Although known for 65 years now [2.2]paracyclophane (**1**) is still far from its retirement age as it still offers lots of opportunities and challenges. The archetype of layered compounds is still fascinating chemists around the world due to its special physical and chemical properties.[1] In fact, it was only very recently, e.g., that the slightly twisted arrangement of the two layered aromatic rings could be proven experimentally.[2] This chiral D_2 symmetric structure, which represents a challenging test case for approximate density functional theory (DFT), has been predicted by high level quantum chemical calculations already 10 years ago.[3] In most cases, substitution of the aromatic rings results in the formation of planar chiral compounds even when the twist in the equilibrium structure is not considered, which could lead to possible diastereomers which influences their CD spectra.[4] For a discussion of possible diastereomers and their CD spectra, see ref 4. Mono- and pseudo-*ortho* 4,12-disubstituted derivatives have found application as chiral building blocks in the synthesis of materials,[5] chiral catalysts,[6] or synthetic receptors.[7] Therefore, it is surprising that pseudo-*meta* 4,15-disubstituted [2.2]-paracyclophanes are largely unexplored, so far, although the 4,15-dibromo-[2.2]paracyclophane (**2**) is easily accessible via bromination of [2.2]paracyclophane and has been known for a long time.[8] In fact only very few 4,15-disubstituted [2.2]-paracyclophanes have been synthesized by D. J. Cram[9] in the early days of paracyclophane-chemistry to study their spectral properties. Despite the work of H. Hopf who brought this class of compounds back into focus in the early 2000s,[8b,10] the number of pseudo-*meta* disubstituted derivatives is still very low. One reason for this might be that research has mainly been focused on the synthesis of the 4,12-derivatives as bidentate ligand or ligand precursors. However, another reason might be that the pseudo-*meta* dibromide was found to be much less reactive compared to its pseudo-*ortho* substitutes isomer concerning a bromine−lithium exchange. This particular reaction is most often used to get access to functionalized derivatives.

Our group has been interested in rigid dissymmetric chiral scaffolds with uncommon stereogenic elements for quite some time now, and we have synthesized and resolved 9,9′-spirobifluorenes with stereogenic spirocenters,[11] Tröger's base derivatives with stereogenic nitrogen atoms,[12] and planar chiral pseudo-*ortho* 4,12-disubstituted [2.2]paracyclophanes[13] and used these for the synthesis of ditopic ligands for the stereoselective self-assembly of metallosupramolecular aggregates.[14] Hence, pseudo-*meta* 4,15-disubstituted [2.2]-paracyclophanes also caught our attention because this substitution pattern brings functional groups in an angle of 120°, which makes them interesting building blocks for the formation of (metallo-)supramolecular aggregates.

Here, we report on the synthesis of various pseudo-*meta* 4,15-disubstituted [2.2]paracyclophanes and the chiral resolution of some complementarily substituted derivatives via semipreparative and preparative HPLC on chiral stationary

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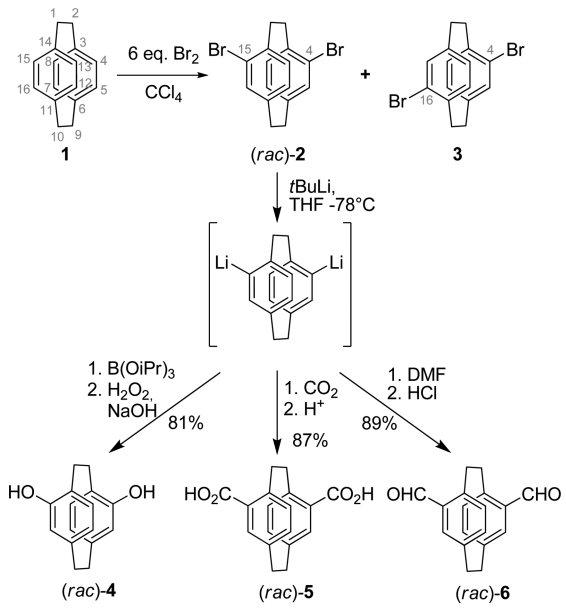
phases. In doing so we were not only able to improve the syntheses of already known compounds such as 4,15-dihydroxy[2.2]paracyclophane,[8b] [2.2]paracyclophane-4,15-dicarboxylic acid,[8b,9] 4,15-diformyl[2.2]paracyclophane,[10] and 4,15-diamino[2.2]paracyclophane,[9] but we could also synthesize the formerly unknown 4,15-diiodo[2.2]paracyclophane, 4,15-di(4,4,5,5-tetramethyl-1,3,2-dioxoborolane)[2.2]paracylcophane, and [2.2]paracyclophane-4,15-diazide, which can easily be converted into the corresponding diamine. Furthermore, we were able to separate the enantiomers of 4,15-dihydroxy[2.2]paracyclophane, [2.2]paracyclophane-4,15-dicarboxylic acid (indirectly in form of its di(4-bromophenyl) ester and subsequent saponification), 4,15-diformyl[2.2]paracyclophane, 4,15-diamino[2.2]paracyclophane, and 4,15-di(4,4,5,5-tetramethyl-1,3,2-dioxoborolane)[2.2]paracyclophane. Enantiomerically pure 4,15-diidodo[2.2]paracyclophane could be obtained via a Sandmeyer reaction from the corresponding enantiomerically pure diamine. The absolute configuration of the resolved compounds could be determined by single crystal X-ray diffraction and/or by comparison of quantum chemically calculated electronic circular dichroism (CD) spectra with experimentally obtained CD spectra.

RESULTS AND DISCUSSION

Our synthesis started from nonsubstituted [2.2]paracyclophane (**1**), which is commercially available and easy to functionalize via well-known bromination.[8a,10] To afford the desired (*rac*)-4,15-dibromo[2.2]paracyclophane {(*rac*)-**2**} we used the method developed by Hopf in 2008,[8b] which also leads to achiral 4,16-dibromo[2.2]paracyclophane (**3**). Compound (*rac*)-**2** then served as our starting material for all further reactions (Scheme 1). The synthesis of compounds (*rac*)-**4**, (*rac*)-**5**, and (*rac*)-**6** has already been reported by H. Hopf,[8b,10] however, only in rather low yields. We tried to follow these procedures but it soon became clear that the bromine−lithium exchange reaction must be the hindered step, which prevents higher yields. Hence, our first task was to improve this step. This was finally achieved by adding a solution of (*rac*)-**2** in dry THF to a solution of *tert*-butyllithium (*t*BuLi) in dry THF at −78 °C. The color of the solution turns from flashy yellow to pale yellow, and after 1 h of stirring at −78 °C the bromine−lithium exchange is complete.

Scheme 1. Synthesis of 4,15-Difunctionalized [2.2]Paracyclophanes by Bromine Lithium Exchange of (*rac*)-2 and Addition of Electrophiles



The synthetic procedure for the preparation of diol (*rac*)-**4** established by H. Hopf et al. allots the use of 2.4 equiv of *n*-butyllithium (*n*BuLi) in diethyl ether at room temperature followed by oxidation of the lithiated (*rac*)-**2** with nitrobenzene at −78 °C to obtain (*rac*)-**4** in 30% yield.[8b] Interestingly, standard addition of $B(OMe)_3$ to the dilithiated intermediate and subsequent oxidative cleavage of the intermediate diboronate did not lead to the desired product. Alternatively, Hopf performed a stepwise synthesis involving monolithiation with 1.2 equiv of *n*BuLi in diethyl ether at room temperature followed by the addition of $B(OMe)_3$ with subsequent oxidation and saponification of the borate leading to the monohydroxy-monobromo compound. This compound was then etherified to protect the hydroxyl-function and subsequently subjected to the complete sequence again to finally obtain the monomethoxy-monohydroxy compound in an overall yield of 65%. With our lithiation approach and the usage of $B(OiPr)_3$ instead of $B(OMe)_3$ we were able to increase the yield of (*rac*)-**4** dramatically to 81%.

Similarly, we were able to improve the synthesis of dicarboxylic acid (*rac*)-**5** to 87% yield which H. Hopf et al. obtained via addition of CO_2 to dilithiated (*rac*)-**2** followed by acidification in 75% yield.[8b]

In 2004 H. Hopf described the synthesis of (*rac*)-4,15-diformyl[2.2]paracyclophane ((*rac*)-**6**) in 62% from (*rac*)-**2** via a bromine−lithium exchange with *sec*-butyllithium (*s*BuLi) in THF followed by the addition of *N*-formylpiperidine and subsequent treatment with aqueous HCl.[10] Again we were able to improve the synthesis by employing *t*BuLi and *N*,*N*-dimethylformamide (DMF) instead and we obtained (*rac*)-**6** after quenching with aqueous HCl in 89% yield.

As we mentioned above our group is interested in enantiomerically pure compounds. Hence, the next challenge was the resolution of the racemic mixtures. As described earlier HPLC on a chiral stationary phase proved to be a versatile method to separate various 4,12-disubstituted [2.2]paracyclophanes.[13] So we tried to apply this approach also for the resolution of the 4,15-disubstituted [2.2]paracyclophanes. In fact, both (*rac*)-**4** and (*rac*)-**6** could be resolved on an analytical and a semipreparative scale in a very effective manner by using a CHIRALPAK IA as the stationary phase and different mixtures of *n*-hexane and ethanol as the eluent (see Supporting Information (SI)). This method allowed us to obtain both enantiomers in optically pure forms on a semipreparative scale.

In case of the dicarboxylic acid (*rac*)-**5** we had to transform it into a corresponding diester first because the acid itself is to polar to allow HPLC on the CHIRALPAK IA stationary phase. So we decided to transfer it into the corresponding 4-bromophenol diester, as it has the right polarity to allow separation and is carrying bromine which should allow us to determine the absolute configuration of the acid via X-ray crystallography if suitable single-crystals can be obtained.

To achieve the esterification the diacid was first transformed into the corresponding dicarboxylic acid chloride upon reaction with oxalyl chloride. This was reacted with 4-bromophenol to afford the desired diester (*rac*)-**7** in 87% yield (Scheme 2). As

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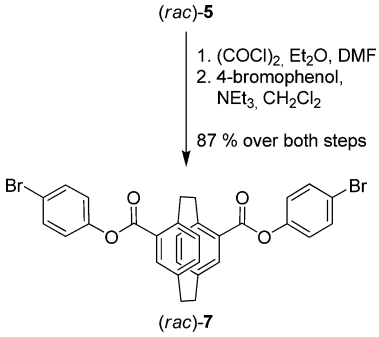
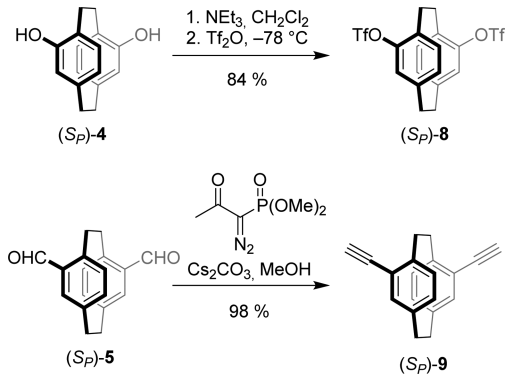
Scheme 2. Synthesis of Di(bromophenyl) Ester (*rac*)-7



hoped, we are also able to resolve the enantiomers in the same way on a semipreparative scale using *n*-hexane/ethanol (80:20 v/v) as the eluent. Saponification of the ester under alkaline conditions then provided the enantiomerically pure acids.

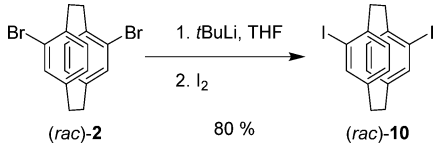
The next step was to use the separated compounds as starting materials for the construction of further functionalized derivatives. Therefore, we decided to transform (*rac*)-**4** into the corresponding ditriflate **8**, which can be used as a coupling reagent in various types of cross-coupling reactions. The enantiomercially pure aldehyde **5** could be transformed into the corresponding dialkyne by treating it with the Bestmann–Ohira[15] reagent following an approach introduced by Hopf.[10] This dialkyne **9** is a promising starting material, e.g., for Sonogashira cross-coupling reactions (Scheme 3).

Scheme 3. Synthesis of Enantiomerically Pure Ditriflate 8 and Enantiomerically Pure Diethynyl-[2.2]paracyclophane 9



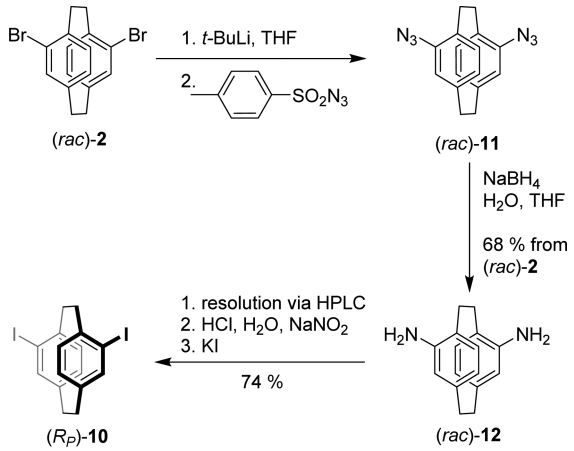
Our next idea was to synthesize the 4,15-diiodo[2.2]-paracyclophane ((*rac*)-**10**), which is also a versatile starting material for various types of transformations including cross-coupling reactions. Again, we performed the bromine–lithium exchange in THF at −78 °C by using *t*BuLi and quenched dilithiated **2** with iodine to get access to the desired diiodinated (*rac*)-**10** in 80% yield (Scheme 4).

Scheme 4. Synthesis of Racemic Diiodo-[2.2]paracyclophane 10



Unfortunately, we were not able to resolve (*rac*)-**10** directly into its enantiomers by HPLC on chiral stationary phases. Hence, we decided to develop a second strategy to synthesize **10** from the corresponding 4,15-diamino[2.2]paracyclophane ((*rac*)-**12**) via a Sandmeyer reaction hoping that this might by easier to resolve via chiral HPLC (Scheme 5).

Scheme 5. Synthesis of Enantiomerically Pure 4,15-Diiodo[2.2]paracyclophane 10 via Racemic Diazide 11 and Racemic Diamine 12 with Subsequent Chiral Resolution via HPLC



The first step is the lithiation of (*rac*)-**2** with subsequent addition of *p*-toluensulfonyl azide leading to the diazide (*rac*)-**11**, which is quite stable and can be purified via column chromatography on silica gel to separate it from *p*-toluensulfonate and defunctionalized [2.2]paracyclophane. Unfortunately, however, we were not able to separate it from the monoazide byproduct at this stage. Hence, the resulting mixture was reduced to the corresponding amines with sodium borohydride, which could easily be separated via column chromatography on silica gel to afford the pure desired diamine (*rac*)-**12** in a good overall yield of 68% starting from dibromide **2**. As hoped, this diamine could be resolved by HPLC on a CHIRALPAK IB column as the stationary phase and *n*-hexane and ethanol (70:30 v/v) as the eluent both on an analytical and a preparative scale. Enantiomerically pure **12** could then be converted into the enantiomerically pure diodide **10** by a Sandmeyer reaction, which was running smoothly without stereochemical leakage to afford the desired product in 74% yield.

Having achieved the syntheses of two enantiomerically pure starting materials for potential cross-coupling reactions (**8** and **10**) and the dialkyne (**9**), which might also serve as the starting material for a transmetalation agent [the reactive Cu-alkyne is formed in situ during a Sonogashira-type cross-coupling reaction], we wanted to broaden the spectrum of versatile precursors for the synthesis of more sophisticated molecular architectures based on the 4,15-difunctionalized [2.2]-paracyclophane motif even further. Thus, we decided to synthesize a [2.2]paracyclophane-4,15-diboronic acid derivative next. Having access to enantiomerically pure starting materials our first approach was the direct formation of the boronic pinacol ester via a Pd-catalyzed Miyaura cross-coupling reaction with bis(pinacolato)diboron,[16] but, unfortunately, this reaction did not lead to the desired product. Also, the boronic acid itself seems to be quite instable, and its synthesis via bromine–

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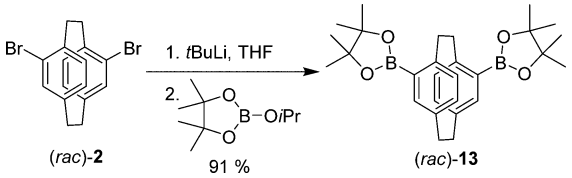
lithium exchange reaction and subsequent borylation with $B(OMe)_3$ or $B(O\textit{i}\text{-}Pr)_3$ followed by ester hydrolysis with aqueous ammonium chloride solution only led to an undefined mixture of products, which neither contained the desired boronic acid nor the nonsubstituted [2.2]paracyclophane. Even the addition of pinacol to the reaction mixture did not provide the boronic ester. This is in agreement with the fact that 4-substituted [2.2]paracyclophane boronicacid esters have been found to be unstable under similar conditions so far. Finally, we were able to solve the problem by using commercially available isopropoxyboronic acid pinacol ester, which is known to react directly with lithiated aromatic molecules to afford the usually rather stable boronic acid pinacol esters.[17]

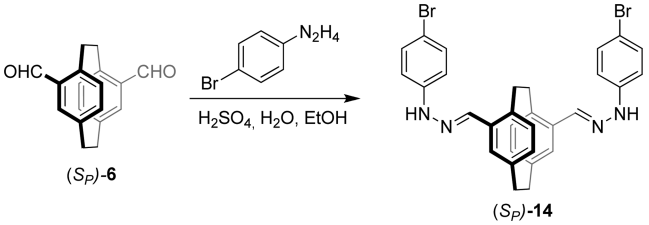
This approach turned out to be very effective, and we were able to prepare the bis(boronic pinacol ester) ((*rac*)-**13**) in an excellent yield of 91%. Fortunately, racemic **13** could also be resolved via HPLC by using a CHIRALPAK IB column as the stationary phase and *n*-hexane/chloroform (98:2 v/v) as the eluent both in analytical and preparative scale (Scheme 6).

Scheme 6. Synthesis of Racemic Diboronic Pinacolatoester 13



Having achieved the successful resolution of racemic **4**, **6**, **7**, **12**, and **13** the final task was to determine the absolute configuration of the isolated enantiomers. A powerful method to determine the absolute configuration is X-ray diffraction analysis of suitable single crystals and the analysis of the Flack parameter. This requires the presence of a heavy atom such as bromine, iodine, or sulfur in the structure, which only applies to compound **7**. Conveniently, **4** can easily be transformed into the corresponding ditriflate **8** and **12** into the corresponding diiodide **10**. To determine the absolute configuration of dialdehyde **6** it was transformed into the corresponding (4-bromophenyl)hydrazone **14** (Scheme 7).

Scheme 7. Synthesis of (+)-(S_P)-14 from Enantiomerically Pure (+)-(S_P)-6



Fortunately, we succeeded in growing single crystals of compounds **7**, **10**, and **14** suitable for XRD-measurements (see SI). Thus, we were able to unambiguously assign the (R_P)-configuration to the (−)-enantiomer of **7**, the (R_P)-configuration to the (−)-enantiomer of **10**, and the (S_P)-configuration to the (+)-enantiomer of **14**. This enabled us also to conclude on the absolute configurations of the enantiomerically pure precursors **5**, **6** and **12**. Hence, (−)-**5** is (R_P)-configurated, (+)-**6** is (S_P)-configurated, and (−)-**12** is (R_P)-configurated.

Unfortunately, we were not successful in growing suitable single crystals of **8** as it turned out to be highly viscous oil in its enantiomerically pure form. Additionally, we could not elucidate the absolute configuration of **13** because of the lack of any heavy atom in the structure. Therefore, we turned our attention to another analytical method that is well established to assign the absolute stereochemistry of enantiomerically pure chiral molecules, the circular dichroism (CD) spectroscopy.

In order to allow an assignment from experimental CD spectra it is probably best to compare them with those obtained from quantum chemical calculations (Figure 1). These calculations were done by employing the recently developed simplified time dependent density functional theory (sTD-DFT) approach.[18] Single point calculations with the global hybrid BHLYP[19] and the range-separated hybrid functional CAM-B3LYP[20] together with the def2-TZVP basis set[21] were performed on TPSS[22]-D3(BJ)[23]def2-TZVP optimized structures. Both functionals reproduce the main features of the experimental spectra, but CAM-B3LYP shows the overall better agreement. The range-separation technique which alleviates so-called self-interaction errors in the density functional improves the quality of the calculated spectra even if CAM-B3LP is not asymptotically correct as it contains 65% exact exchange in the long-range limit. In case of (−)-(S_P)-**4**, (+)-(S_P)-**6** and (+)-(S_P)-**13** a small shift of the computed vertical excitation energies by −0.2 to −0.3 eV is observed, which is typical for this functional together with the sTD-DFT approach (spectra for all four compounds including the rotatory strengths for CAM-B3LYP are provided in the Supporting Information). For a more detailed discussion of the CD spectra of [2.2]-paracyclophanes, see ref 4.

Given the fact that all (−)-enantiomers described above were found to be (R_P)-configurated we were initially surprised to find that that comparison of the experimental and simulated spectra clearly proved that the (−)-enantiomer of compound **4** is indeed (S_P)-configurated. Hence, we decided to validate our theoretical approach by also applying it to the simulation of the spectra of **6** and **10** whose configuration we could already assign via single crystal X-ray diffraction. These calculations nicely agree with calculated spectra and corroborate the assignment made according to the X-ray diffraction analysis.

Having proved that the applied quantum chemical method is indeed reliable, we were also able to determine the absolute configuration of boronic ester **13** showing that the (+)-enantiomer is again (S_P)-configurated.

CONCLUSION

In summary we have synthesized 12 planar chiral 4,15-difunctionalized [2.2]paracyclophanes. Some of them (**2**, **4**–**6**, **9**, and **12**) have been prepared in racemic form before, but some of them (**8**, **10**, **11**, **13**, and **14**) have not been reported yet. By improving the efficiency of the bromine–lithium exchange we have been able to dramatically increase the yields of **4**–**6** and **12**. Furthermore, we have been able to resolve five of these compounds (**4**, **6**, **7**, **12**, and **13**) by HPLC techniques on an analytical, semipreparative and preparative scale by using CHIRALPAK IA and CHIRALPAK IB stationary phases. The absolute configuration could be assigned by X-ray crystal structure analysis of **7**, **10**, and **14**, which also implies the absolute configuration of **5**, **6**, and **12**. The absolute configuration of **4** and **13** was determined by comparison of

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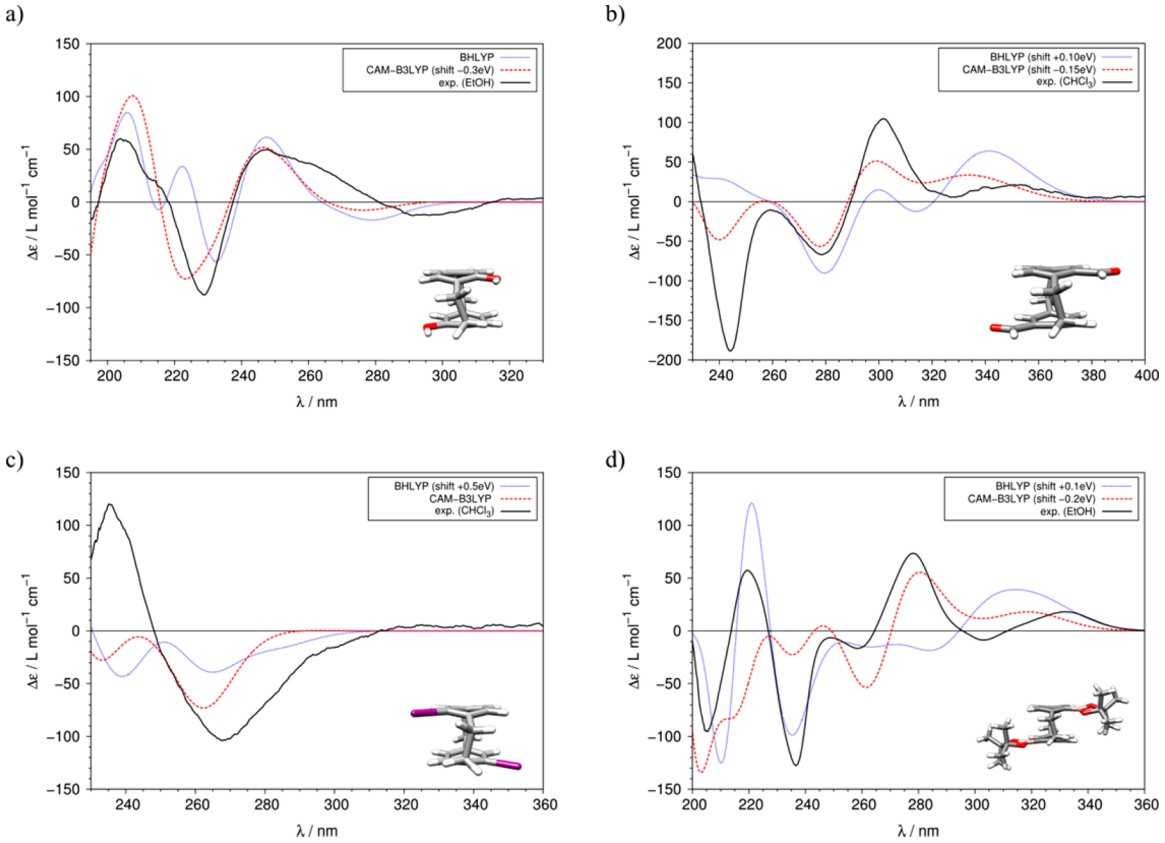

Figure 1. Experimental and simulated CD spectra of a) (−)-(S_P)-**4**, b) (+)-(S_P)-**6**, c) (−)-(R_P)-**10**, and d) (+)-(S_P)-**13**.

experimental CD-spectra with quantum chemically calculated ones. This method was validated by comparing experimental and simulated CD spectra of **6** and **10** with known configuration. Most of the derivatives carry versatile functional groups that offer the possibility to integrate the 4,15-difunctionalized [2.2]paracyclophane skeleton into more sophisticated (supra-)molecular architectures with well-defined stereochemical properties.

EXPERIMENTAL SECTION

General Information. All reactions with moisture or air sensitive substances were performed under argon according by using Schlenk techniques with oven-dried glass ware. Thin-layer chromatography was performed with aluminum TCL plates (silica gel 60F_{254}). Detection was carried out under UV light with 254 and 366 nm. Products were purified via column chromatography by using silica gel 60 (70−230 mesh). ^{1}H NMR chemical shifts are reported on the δ scale (ppm) relative to residual nondeuterated solvent as the internal standard. The ^{13}C {^{1}H} NMR chemical shifts are reported on the δ scale (ppm) relative to deuterated solvent as the internal standard. Signals were assigned on the basis of ^{1}H, ^{13}C, H,H−COSY, HMQC, and HMBC NMR experiments. Mass spectra were recorded as EI or as QToF-ESI spectra. Chiral analytical and semipreparative stationary phases CHIRALPAK IA (column size 0.46 cm × 25 cm respectively 1 cm × 25 cm, equipped with precolumns of the same diameter and 2 cm length) and chiral analytical and preparative stationary phases CHIRALPAK IB (column size 0.46 cm × 25 cm respectively 2.5 cm × 20 cm, equipped with precolumns of the same diameter and 2 cm length) were applied and solvent mixtures of *n*-heptane (HPLC quality) and chloroform (p.a. stabilized with ethanol) and *n*-hexane (HPLC qualitiy) and ethanol (p.a.) and 2-propanol (HPLC quality) were used. Circular dichroism spectroscopy was performed using ethanol or chloroform (p.a.) as solvents.

Most solvents were dried, distilled and stored under argon according to standard procedures. All chemicals were used as received from commercial sources. (*rac*)-4,15-Dibromo[2.2]paracyclophane[8b] was prepared according to a literature protocol.

(*rac*)-4,15-Dihydroxy[2.2]paracyclophane {(*rac*)-4}. 7.20 mL of *t*BuLi (1.9 M in pentane, 13.70 mmol) were added to 40 mL of dry THF at −78 °C and stirred for 5 min. To the flashy yellow solution (*rac*)-**2** (1.00 g, 2.74 mmol) dissolved in THF (20 mL) was added via a syringe. The mixture is stirred for 1 h at −78 °C turning from flashy yellow to pale yellow. Then B(O*i*Pr)$_3$ (2.06 g, 2.53 mL, 10.96 mmol) was added, and the solution was allowed to slowly warm to room temperature turning from yellow to colorless, and precipitate was formed. Subsequently aqueous KOH (0.5 M, 2.74 mL, 1.38 mmol) and H_2O_2 (35%, 2.00 mL, 21.92 mmol) were added, and the solution was stirred for 1 h. The reaction mixture was poured into water and was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were evaporated, and crude **4** was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1 (v/v); R_f = 0.6), yield 0.53 g (2.22 mmol, 81%). The product is a white solid: mp 227 °C (decomposing); ^{1}H NMR (500.1 MHz, acetone-d_6, 298 K) δ = 2.67−2.76 (m, 2 H, H-1, H-2), 2.79−2.82 (m, 4 H, H-9, H-10), 3.15−3.22 (m, 2 H, H-1, H-2), 5.67 (d, $^4J_{5,7}$ = $^4J_{16,\ 12}$ = 1.7 Hz, 2 H, H-5, H-16), 6.08 (dd, $^3J_{7,\ 8}$ = $^3J_{12,13}$ = 7.6 Hz, $^4J_{7,5}$ = $^4J_{12,16}$ = 1.7 Hz, 2 H, H-7, H12), 6.83 (d, $^3J_{8,7}$ = $^3J_{13,12}$ = 7.6 Hz, 2 H, H-8, H-13) 7.64 (s, 2 H, O−H) ppm; ^{13}C {^{1}H} NMR (125.8 MHz, acetone-d_6, 298 K) δ = 30.5 (C-1, C-2), 35.0 (C-9, C-10), 121.71 (C-5, C-16), 124.1 (C-7, C-12), 126.7 (C-3, C-14), 130.8 (C-8, C-13), 141.4 (C-6, C-11), 156.6 (C-4, C-15) ppm; MS (EI) *m*/*z* (%) = 240.1 (70) $[C_{16}H_{16}O_2]^{+\bullet}$, 120.1 (100) $[C_7H_8O]^+$, 91 (20) $[C_7H_7]^+$; EI-HRMS *m*/*z* calcd. for $[C_{16}H_{16}O_2]^{+\cdot}$ 240.1150, found 240.1157.

Separation of Enantiomers. HPLC [chiral phase (semipreparative): CHIRALPAK IA; *n*-hexane/EtOH (90:10); *f* = 5.0 mL/min; loading 20 mg of racemic material per run] t_R = 12.80 [(+)-(R_P)-**4**

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$[\alpha]_D^{20}$ = +37.0 (c = 4.4645 g/mL, THF), >99.9% *ee*], 15.23 [(−)-(S_P)-**4** $[\alpha]_D^{20}$ = −35.8 (c = 4.4605 g/mL, THF), 99.8% *ee*] min.

(R_P)- and (S_P)-[2.2]Paracyclophane-4,15-dicarboxylic acid {(R_P)- and (S_P)-5}. KO*t*Bu (0.337 g, 3.00 mmol) was dissolved in water (0.54 mL, 3.00 mmol), and THF (40 mL) and enantiomerically pure (R_P)- or (S_P)-**8** (0.150 g, 0.25 mmol) was added. The resulting mixture was stirred overnight. The THF was evaporated and water was added. The mixture was acidified with aq. HCl (2 M), and the white precipitated was filtered off and washed with water to give the enantiomerically pure target compound. Yield: 0.057 g (0.19 mmol, 77%). The product is a white solid: mp >250 °C; ^{1}H NMR (400.1 MHz, DMSO d_6, 293 K) δ = 2.83−2.94 (m, 2 H, H-1, H-2), 2.94−3.05 (m, 2 H, H-9, H-10), 3.09−3.21 (m, 2H, H-9, H-10), 3.89−4.02 (m, 2 H, H-1, H-2), 6.47 (d, $^3J_{8,7}$ = $^3J_{13,12}$ = 7.8 Hz, 2 H, H-8, H-13), 6.62 (dd, $^3J_{7,8}$ = $^3J_{12,13}$ = 7.8 Hz, $^4J_{7,5}$ = $^4J_{12,16}$ = 2.0 Hz, 2 H, H-7, H12) 7.13 (d, $^4J_{5,7}$ = $^4J_{16,12}$ = 2.0 Hz, 2 H, H-5, H-16), 12.59 (s, 2 H, CO_2−H) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, DMSO d_6, 293 K) δ = 34.1 (C-1, C-2), 35.1 (C-9, C-10), 131.5 (C-4, C-15), 133.8 (C-5, C-16), 135.1 (C-8, C-13), 135.7 (C-7, C-12), 139.8 (C-6, C-11), 142.2 (C-3, C-14), 176.9 (CO_2H) ppm; MS (ESI negative mode) m/z (%) = 295.1 (100) $[C_{18}H_{15}O_4]^-$; ESI-HRMS m/z calcd. for $[C_{18}H_{15}O_4]^-$ 295.0976, found 295.0978.

Compound (+)-(S_P)-**5**: $[\alpha]_D^{20}$ = +65.6 (c = 4.11 mg/mL, EtOH). Compound (−)-(R_P)-**5**: $[\alpha]_D^{20}$ = −68.2 (c = 4.40 mg/mL, EtOH).

(*rac*)-4,15-Diformyl[2.2]paracyclophane {(*rac*)-6}. 7.20 mL of *t*BuLi (1.9 M in pentane, 13.70 mmol) were added to 40 mL of dry THF at −78 °C and stirred for 5 min. To the flashy yellow solution (*rac*)-**2** (1.00 g, 2.74 mmol) dissolved in THF (20 mL) was added via a syringe. The mixture was stirred for 1 h at −78 °C turning from flashy yellow to pale yellow. Then DMF (0.72 g, 0.76 mL, 10.00 mmol) was added, and the solution was allowed to slowly warm to room temperature turning from yellow to colorless. Subsequent aqueous HCl (4 M, 7.5 mL, 30 mmol) was added, and the mixture was stirred for further 30 min. Water and Et_2O were added, and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic phases were washed with 0.5 M HCl, saturated aqueous $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and crude **6** was purified via column chromatography on silica gel (cyclohexane/ethyl acetate, 5:1, v/v) R_f = 0.6), yield 0.645 mg (2.44 mmol, 89%). The product is a white solid. The analytical data were in accordance with the literature data.[10]

Separation of Enantiomers. HPLC [chiral phase (semipreparative): CHIRALPAK IA; *n*-hexane/EtOH (90:10); f = 5.0 mL/min; loading 30 mg of racemic material per run] t_R = 14.53 [(+)-(S_P)-**6** $[\alpha]_D^{20}$ = +231.2 (c = 4.645 g/mL, THF), >99.9% *ee*], 18.76 [(−)-(R_P)-**6** $[\alpha]_D^{20}$ = −226.3 (c = 4.715 g/mL, THF), >99.9% *ee*] min.

(*rac*)-Di(4-bromophenyl)[2.2]paracyclophane-4,15-dixarboxylate {(*rac*)-7}. (*rac*)-**6** (0.200 g, 0.64 mmol) was dissolved in dry diethyl ether (40 mL). Oxalyl chloride (0.12 mL, 1.48 mmol) and one drop of DMF were added, and the resulting mixture was stirred for 2 h at room temperature. The solvent was evaporated, and the white residue was dissolved in dry dichloromethane (10 mL). Subsequently dry triethylamine (10 mL) was added, and the solution turned red. After that 4-bromophenol (0.463 g, 2.68 mmol) was added, and the solution turned yellow. The solution was stirred at room temperature overnight and then poured into ice water. The mixture was acidified, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine and dried over Mg_2SO_4. The product was obtained as a white powder. If needed it can be further purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 2:1 (v/v), R_f = 0.8). The product was obtained as a white powder. Yield: 0.356 g (0.59 mmol, 92%); mp 94 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 293 K) δ = 3.08−3.17 (m, 4 H, H-1, H-2, H-9, H-10), 3.22−3.33 (m, 2 H, H-9, H-10), 4.08−4.15 (m, 2 H, H-1, H-2), 6.71 (d, 2 H, H-8, H-13, $^3J_{8,7}$ = $^3J_{13,12}$ = 7.9 Hz), 6.75 (dd, 2 H, H-7, H-12 $^3J_{7,8}$ = $^3J_{12,13}$ = 7.9 Hz, $^4J_{7,5}$ = $^4J_{12,16}$ = 1.9 Hz), 7.15 (d, 4 H, H-phenyl ^3J = 8.9 Hz), 7.39 (d, 2 H, H-5, H-16 $^4J_{5,7}$ = $^4J_{16,12}$ = 1.9 Hz) 7.59 (d, 4 H, H-phenyl ^3J = 8.9 Hz) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$, 293 K) δ = 34.9 (C-9, C-10), 35.8 (C-1, C-2), 119.2 (C-21), 123.7 (C-19), 130.1 (C-4, C-15), 132.8 (C-20), 134.6 (C-8, C-13), 135.7 (C-5, C-12), 137.0 (C-7, C-12), 140.8 (C-6, C-11), 144.3 (C-3, C-14), 150.0 (C-18), 165.0 (C-17) ppm; MS (EI) m/z (%) 606.0 (5) $[C_{30}H_{22}Br_2O_4]^{+\cdot}$, 433.0 (100) $[C_{24}H_{18}BrO_3]^+$, 131.0 (70) $[C_9H_7O]^+$; ESI-HRMS m/z calcd. for $[C_{30}H_{22}O_4Br_2]^+$ 603.9885, found 603.9880. Elemental analysis calcd (%) for $C_{30}H_{22}O_4Br_2$ (606.30) C 59.43, H 3.66. Found: C 59.21, H 3.91.

Separation of Enantiomers. HPLC [chiral phase (semipreparative): CHIRALPAK IA; *n*-hexane/EtOH (80:20); f = 5.0 mL/min; loading 20 mg of racemic material per run] t_R = 10.63 [(+)-(S_P)-7 $[\alpha]_D^{20}$ = +164.8 (c = 3.405 g/mL, THF), 99.9% *ee*], 14.27 [(−)-(R_P)-7 $[\alpha]_D^{20}$ = −161.3 (c = 4.080 g/mL, THF), 99.7% *ee*] min.

(R_P)- and (S_P)-4,15-Di(trifluoromethanesulfonate)[2.2]-paracyclophane {(R_P)- and (S_P)-8}. Enantiomerically pure (S_P)- or (R_P)-**4** (0.200 g, 0.83 mmol) was dissolved in dry triethylamine (1.15 mL, 8.30 mmol) and dry CH_2Cl_2 (20 mL). The solution was cooled to −78 °C, and triflic anhydride (0.35 mL, 2.08 mmol) was added slowly via syringe. The reaction mixture was allowed to warm to room temperature. After that the solution was acidified with aq. HCl (2 M), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. The solvents were evaporated, and the crude product was purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 2:1 (v/v); R_f = 0.7). The product was obtained a colorless highly viscous oil, whereas (*rac*)-**8** was obtained as a pale yellow solid (mp 77 °C). Yield: 0.352 g (0.70 mmol, 84%); ^{1}H NMR (400.1 MHz, $CDCl_3$, 293 K) δ = 2.92−3.01 (m, 2 H, H-1, H-2), 3.04−3.13 (m, 4 H, H-9, H-10), 3.32−3.41 (m, 2 H, H-1, H-2), 6.23 (d, $^4J_{5,7}$ = $^4J_{16,12}$ = 1.7 Hz, 2 H, H-5, H-16), 6.61 (dd, $^3J_{7,8}$ = $^3J_{12,13}$ = 8.0 Hz, $^4J_{7,5}$ = $^4J_{12,16}$ = 1.7 Hz, 2 H, H-7, H12), 7.02 (d, $^3J_{8,7}$ = $^3J_{13,12}$ = 8.0 Hz, 2 H, H-8, H-13) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$, 293 K) δ = 30.4 (C-1, C-2), 34.4 (C-9, C-10), 120.4 [CF_3, $^1J_{C,F}$ = 318 Hz], 127.5 (C-5, C-16), 132.0 (C-3, C-14), 132.1 (C-7, C-12), 132.7 (C-8, C-13), 142.8 (C-6, C-11), 148.7 (C-4, C-15) ppm; MS (EI) m/z (%) = 504.0 (30) $[C_{18}H_{14}F_6O_6S_2]^{+\bullet}$, 371.0 (40) $[C_{17}H_{14}O_4F_3S]^+$, 252.0 (100) $[C_9H_7O_3F_3S]^+$, 91 (25) $[C_7H_7]^+$; EI-HRMS m/z calcd. for $[C_{18}H_{14}F_6O_6S_2]^{+\cdot}$ 504.0136, found 504.0136.

Compound (+)-(S_P)-**8**: $[\alpha]_D^{20}$ = +16.7 (c= 8.050 mg/mL, $CHCl_3$). Compound (−)-(R_P)-**8**: $[\alpha]_D^{20}$ = +17.3 (c = 4.180 mg/mL, $CHCl_3$).

(R_P)- and (S_P)-4,15-Diethynyl[2.2]paracyclophane {(R_P)- and (S_P)-(9)}. Enantiomerically pure (R_P)- or (S_P)-**6** (0.500 g, 1.89 mmol) and Cs_2CO_3 (2.407 g, 7.56 mmol) were suspended in anhydrous MeOH (40 mL), and the Bestmann−Ohira reagent (1.390 g, 7.56 mmol) was added. The resulting mixture was stirred for 24 h at room temperature. Subsequently another portion of Cs_2CO_3 (0.722 g, 2.52 mmol) and the Bestmann−Ohira reagent (0.463 g, 2.52 mmol) was added and stirred for further 12 h. After that CH_2Cl_2 and water were added, and the layers were separated. The aqueous layer was extracted CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the crude product was purified, if necessary, by column chromatography on silica gel (eluent: 5% of ethyl acetate in cyclohexane, R_f = 0.8). The product was obtained as a pale yellow powder. Yield: 0.475 g (1.85 mmol, 98%). The analytical data were in accordance with the literature data.[10]

Compound (+)-(S_P)-**9**: $[\alpha]_D^{20}$ = +339 (c= 2.760 mg/mL, $CHCl_3$). Compound (−)-(R_P)-**9**: $[\alpha]_D^{20}$ = −342 (c= 2.355 mg/mL, $CHCl_3$).

(*rac*)-4,15-Diiodo[2.2]paracyclophane {(*rac*)-10}. 7.20 mL of *t*BuLi (1.9 M in pentane, 13.70 mmol) were added to 40 mL of dry THF at −78 °C and stirred for 5 min. To the flashy yellow solution (*rac*)-**2** (1.000 g, 2.74 mmol) dissolved in THF (20 mL) was added via a syringe. The mixture is stirred for 1 h at −78 °C turning from flashy yellow to pale yellow. Then iodine (1.905 g, 7.50 mmol) was added. The solution was allowed to slowly warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 and water, and the layers separated. The organic layer was washed with saturated aqueous Na_2SO_3, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the crude product was purified by column

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chromatography on silica gel (eluent: cyclohexane, R_f = 0.7). The product is a white powder. Yield: 2.060 g (4.34 mmol, 80%); mp 161 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 293 K) δ = 2.84−2.92 (m, 2 H, H-1, H-2), 3.03−3.20 (m, 2 H, H-1, H-2), 3.21−3.22 (m, 4 H, H-9,H-10), 6.50 (dd, 2 H, H-7, H-12, $^3J_{7,8} = {}^3J_{12,13}$ = 7.8 Hz, $^4J_{7,5} = {}^4J_{12,16}$ = 1.8 Hz),6.91 (d, 2 H, H-5, H-16, $^4J_{5,7} = {}^4J_{16,12}$ = 1.8 Hz) 7.20 (d, 2 H, H-8, H-13, $^3J_{8,7} = {}^3J_{13,12}$ = 7.8 Hz) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$, 293 K δ = 34.8 (C-1, C-2), 36.9 (C-9, C-10), 104.9 (C-4, C-15), 129.5 (C-8, C-13), 131.9 (C-7, C-12), 141.0 (C-6, C-11), 142.7 (C-3, C-14), 142.8 (C-5, C-16); MS (EI) m/z (%) 459.9 (100) $[C_{16}H_{14}I_2]^+$, 229.9 (60) $[C_8H_7I]^+$; ESI-HRMS m/z calcd. for $[C_{16}H_{14}I_2]^+$ 459.9185, found 459.9192.

(R_P)-4,15-Diiodo[2.2]paracyclophane {(R_P)-(10)}. Enantiomerically pure (R_P)-**12** (0.100 g, 0.43 mmol) was dissolved in conc. HCl (1.5 mL) and diluted with water (5 mL). The stirred solution was cooled to 0 °C and $NaNO_2$ (0.070 g, 1.03 mmol) dissolved in water (2.5 mL) was slowly added. After 30 min. KI (0.374 g, 2.25 mmol) dissolved in water (2 mL) was added at 0 °C. The solution was stirred at 0 °C for 30 min and was then heated to 80 °C for 2 h. After cooling to room temperature the solution was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with saturated aqueous $NaHSO_3$ solution and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and crude **10** was purified by column chromatography on silica gel (eluent: cyclohexane, R_f = 0.7). The product is a white powder. Yield: 0.152 g (0.32 mmol, 74%). Suitable crystals for X-ray diffraction analysis were grown from a mixture of cyclohexane and ethyl acetate.

Compound (−)-(R_P)-**10**: $[\alpha]_D^{20}$ = −245 (c = 3.20 mg/mL, $CHCl_3$).

(*rac*)-[2.2]Paracyclophane-4,15-diazide {[*rac*)-11}. 7.20 mL of *t*BuLi (1.9 M in pentane, 13.70 mmol) were added to 40 mL of dry THF at −78 °C and stirred for 5 min. To the flashy yellow solution (*rac*)-**3** (1.000 g, 2.74 mmol) dissolved in THF (20 mL) was added via a syringe. The mixture was stirred for 1 h at −78 °C turning from flashy yellow to pale yellow. Then *p*-toluenesulfonyl azide (1.608 g, 8.16 mmol) in 10 mL of dry THF was added slowly to the stirred solution. The solution was allowed to slowly warm to room temperature, turning from pale yellow to red and then to black. The reaction mixture is poured into saturated ammonium chloride solution, and the aqueous layer was extracted with dichloromethane (3 × 60 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and crude **11** was purified via column chromatography on silica gel (cyclohexane, R_f = 0.4) to remove remaining *p*-toluenesulfonate. The mixture still contains monoazide byproduct. The product mixture is a pale yellow solid: ^{1}H NMR (400.1 MHz, $CDCl_3$, 293 K) δ = 2.75−2.84 (m, 2 H, H-1, H-2), 2.99−3.12 (m, 4 H, H-1, H-9), 3.14−3.23 (m, 2 H, H-1, H-2), 6.01 (d, 2 H, H-5, H-16 $^4J_{5,7} = {}^4J_{16,12}$ = 1.7 Hz), 6.38 (dd, 2 H, H-7, H-12, $^3J_{7,8} = {}^3J_{12,13}$ = 7.9 Hz, $^4J_{7,5} = {}^4J_{12,16}$ = 1.7 Hz), 6.84 (d, 2 H, H-8, H-13, $^3J_{8,7} = {}^3J_{13,12}$ = 7.9) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$, 293 K) δ = 30.8 (C-1, C-2), 34.7 (C-9, C-10), 123.8 (C-5, C-16), 128.0 (C-7, C-12), 131.1 (C-8, C-13), 133.2 (C-3, C-14), 140.8 (C-6, C-11), 146.2 (C-4, C-15) ppm; MS (EI) m/z (%) = 290.1 (25) $[C_{16}H_{14}N_6]^{+\bullet}$; EI-HRMS m/z calcd. for $[C_{16}H_{14}N_6]^{+\cdot}$ 290.1280, found 290.1282.

(*rac*)-4,15-Diamino[2.2]paracyclophane {(*rac*)-12}. A round-bottom flask was charged with tetrabutylammonium iodide (1.272 g, 3.44 mmol) and $NaBH_4$ (2.612 g, 68.80 mmol) under an argon atmosphere. Subsequently, (*rac*)-**11** (1.000 g, 3.44 mmol), dissolved in 26.5 mL of dry THF, and 21.8 mL of water were added, and the solution was stirred for 48 h at room temperature. Afterward additionally $NaBH_4$ (1.306 g, 34.40 mmol) was added, and the mixture was stirred for further 24 h. The reaction mixture was then poured into water and was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and crude **12** was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1, v/v + 5% triethylamine, R_f = 0.5), yield 0.729 g (3.06 mmol, 73%). The product is a brownish solid: mp 232 °C; ^{1}H NMR (400.1 MHz, CD_2Cl_2, 293 K) δ = 2.76−2.80 (m, 4 H, H-1*, H-2*), 2.83−2.97 (m, 4 H, H-9*, H-10*), 3.35 (bs, 4H, N−H), 5.45 (d, 2 H, H-5, H-16, $^4J_{5,7} = {}^4J_{16,12}$ = 1.8 Hz), 5.97 (dd, 2 H, H-7, H-12, $^3J_{7,8} = {}^3J_{12,13}$ = 7.7 Hz, $^4J_{7,5} = {}^4J_{12,16}$ = 1.8 Hz), 6.92 (d, 2 H, H-8, H-13, $^3J_{8,7} = {}^3J_{13,12}$ = 7.7 Hz) ppm; ^{13}C {^{1}H} NMR (100.6 MHz, CD_2Cl_2, 293 K) δ = 29.7 (C-1*, C-2*), 35.0 (C-9*, C-10*), 120.7 (C-5, C-16), 122.3 (C-7, C-12), 124.0 (C-3, C-14), 128.7 (C-8, C-13), 140.8 (C-6, C-11), 146.2 (C-4, C-15) ppm (* assignment might be interchanged); MS (EI) m/z (%) = 238.1 (50) $[C_{16}H_{18}N_2]^{+\bullet}$, 119.0 (100) $[C_8H_9N]^+$, 91 (10) $[C_7H_7]^+$; EI-HRMS m/z calcd. for $[C_{16}H_{18}N_2]^{+\cdot}$ 238.1470, found 238.1472.

Separation of Enantiomers. HPLC [chiral phase (semipreparative): CHIRALPAK IB; *n*-hexane/EtOH (70:30); f = 20.0 mL/min; loading 40 mg of racemic material per run] t_R = 11.86 [(+)-(S_P)-**12** $[\alpha]_D^{20}$ = +95 (c = 2.55 g/mL, THF), 99.9% *ee*], 15.55 [(−)-(R_P)-**12** $[\alpha]_D^{20}$ = −97 (c = 3.15 g/mL, THF), 99.9% *ee*] min.

(*rac*)-4,15-Di-(4,4,5,5-tetramethyl-1,3,2-dioxborolan)-[2.2]-paracylcophane {(*rac*)-13}. 7.20 mL of *t*BuLi (1.9 M in pentane, 13.70 mmol) were added to 40 mL of dry THF at −78 °C and stirred for 5 min. To the flashy yellow solution (rac)-**3** (1.000 g, 2.74 mmol) dissolved in THF (20 mL) was added via a syringe. The mixture was stirred for 1 h at −78 °C turning from flashy yellow to pale yellow. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.530 g, 1.66 mL, 8.22 mmol) in 10 mL of dry THF was added, and the solution was allowed to slowly warm to room temperature, thereby first turning to pale green and then colorless. The reaction was quenched by the addition of water and ethyl acetate. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic phases were washed with water and brine and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 10:1 v/v, R_f = 0.5), yield 1.196 g (2.60 mmol, 95%). The product is a white powder: mp 190 °C; ^{1}H NMR (400.1 MHz, acetone-d_6, 293 K) δ = 1.41 (s, 12 H, CH_3), 2.86−2.94 (m, 2H, H-1, H-2), 2.95−3.05 (m, 2H, H-9, H-10), 3.10−3.20 (m, 2H, H-9, H-10), 3.85−3.95 (m, 2H, H-1, H-2), 6.37 (d, 2H, H-8, H-13, $^3J_{8,7} = {}^3J_{13,12}$ = 7.7 Hz), 6.52 (dd, 2H, H-7, H12, $^3J_{7,8} = {}^3J_{12,13}$ = 7.7 Hz, $^4J_{7,5} = {}^4J_{12,16}$ = 2.0 Hz), 7.00 (d, $^4J_{5,7} = {}^4J_{16,12}$ = 2.0 Hz, 2H, H-5, H-16), ppm; ^{13}C {^{1}H} NMR (100.4 MHz, acetone-d_6, 293 K) δ = 24.8 (CH_3), 25.1 (CH_3), 35.39 (C-1, C-2), 36.42 (C-1, C-2), 83.6 ($C_{quaternary}$), 134.3 (C-8, C-13), 135.3 (C-7, C-12), 138.8 (C-6, C-11), 140.9 (C-5, C-16), 148.0 (C-3, C-14) ppm. The carbon connected to the boron cannot be seen in the NMR spectrum because of its low intensity due to the coupling to the boron. ^{11}B {^{1}H} NMR (128.4 MHz, acetone-d_6, 293 K) 31.23 (bs) ppm; MS (ESI) m/z (%) = 461.3 (50) $[C_{28}H_{38}B_2O_4+H]^{+\bullet}$, 483.3 (100) $[C_{28}H_{38}B_2O_4+Na]^+$; ESI-HRMS m/z calcd. for $[C_{28}H_{38}B_2O_4+Na]^+$ 483.2858, found 483.2863. Elemental analysis calcd (%) for $C_{28}H_{38}B_2O_4$ (460.22): C 73.07, H 8.32. Found: C 72.96, H 8.18.

Separation of Enantiomers. HPLC [chiral phase (preparative): CHIRALPAK IB; *n*-hexane/$CHCl_3$ (98:2); f = 9.0 mL/min; loading 10 mg of racemic material per run] t_R = 15.03 [(+)-(S_P)-**13** $[\alpha]_D^{20}$ = +158 (c = 2.010 g/mL, EtOH), >99.9% *ee*], 17.48 [(−)-(R_P)-**13** $[\alpha]_D^{20}$ = −158 (c = 2.29 g/mL, EtOH), 98.7% *ee*] min.

(S_P)-4,15-Di{(4-bromophenyl)hydrazone}[2.2]paracyclophane {(S_P)-14}. 4-Bromohydrazine (0.45 g) was dissolved in conc. H_2SO_4 (2 mL) and water (3 mL). EtOH (10 mL) was added to this solution and precipitate was filtered off. (S_P)-**5** (0.100 g, 0.273 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to the 4-bromohydrazine solution. After keeping at room temperature overnight greenish crystals were formed, which were filtered off and carefully washed with water. These crystals were suitable for X-ray diffraction analysis: mp 218 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 293 K) δ = 2.87−2.97 (m, 2 H, H-1, H-2), 2.98−3.09 (m, 2 H, H-9, H-10), 3.10−3.21 (m, 2 H, H-9, H-10), 3.69−3.80 (m, 2 H, H-1, H-2) 6.45 (d, 2 H,H-7, H-12, $^3J_{7,8} = {}^3J_{12,13}$ = 7.7 Hz), 6.59 (d, 2 H, H-8, H-13, $^3J_{8,7} = {}^3J_{13,12}$ = 7.7 Hz), 6.86 (s, 2 H, H-5, H-16), 7.03 (d, 4 H, H-phenyl, ^3J = 8.8 Hz), 7.41 (d, 4 H, H-phenyl, ^3J = 8.8 Hz), 7.68 (s, 2 H, CHN) ppm; MS (ESI) m/z (%) 601.06 (100) $[C_{30}H_{26}Br_2N_4+H]^+$, 623.0 (35) $[C_{30}H_{26}Br_2N_4+Na]^+$; ESI-HRMS m/z calcd. for $[C_{30}H_{26}Br_2N_4+H]^+$ 601.0597, found 601.0574. Elemental analysis calcd (%) for $C_{30}H_{26}Br_2N_4$ (602.36)•2 H_2O: C 56.44, H 4.74. Found: C 56.89, H 4.75.

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Table 1. Crystallographic Data for (−)-(R_P)-7, (−)-(R_P)-10, and (+)-(S_P)-14

parameters	(−)-(R_P)-7	(−)-(R_P)-**10**	(+)-(S_P)-**14**
formula	$C_{30}H_{22}Br_2O_4$	$C_{16}H_{14}I_2$	$C_{30}H_{26}Br_2N_4$
M_r	606.30	460.07	602.37
T [K]	123(2)	123(2)	123(2)
crystal system	orthorhombic	trigonal	monoclinic
space group	$P22_12_1$	$P3_2$	$C2$
crystal dimensions [mm]	0.60 × 0.12 × 0.02	0.36 × 0.24 × 0.18	0.24 × 0.08 × 0.04
a [Å]	6.8010(2)	11.6253(2)	33.742(2)
b [Å]	16.1651(5)	11.6253(2)	7.9547(3)
c [Å]	22.3501(8)	9.0313(2)	9.8768(7)
α [°]	90	90	90
β [°]	90	90	97.566(2)
γ [°]	90	120	90
V [Å^3]	2457.14(14)	1057.04(5)	2627.9(3)
Z	4	3	4
ρ [mg m^3]	1.639	2.168	1.523
μ [mm^{-1}]	3.335	4.442	3.111
θ range [°]	2.68−28.00	3.03−28.00	2.44−27.86
completeness [%]	98.6	99.9	98.0
reflections measured	17603	19608	8898
unique reflections (R_{int})	5763 (0.0856)	3396 (0.0404)	5504 (0.0455)
data/restrains/parameters	5763/0/325	11266/19/649	5504/85/325
GoF on F^2	0.996	1.088	0.937
final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0389	$R1$ = 0.0238	$R1$ = 0.0382
	$\omega R2$ 0.0826	$\omega R2$ = 0.0588	$\omega R2$ = 0.0789
R indices all data	$R1$ = 0.0515	$R1$ = 0.0244	$R1$ = 0.0572
	$\omega R2$ 0.0867	$\omega R2$ = 0.0590	$\omega R2$ = 0.0842
absolute structure parameter X	−0.013(8)	−0.04(3)	0.000(9)

Compound (+)-(S_P)-**14**: $[\alpha]_D^{20}$ = +1056 (c= 4.42 mg/mL, THF).

Crystal Structure Determinations. Data were collected on a Nonius KappaCCD diffractometer equipped with a low temperature device (Cryostream, Oxford Cryosystems, 600er series) using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Intensities were measured by fine-slicing ω- and φ-scans and corrected for background, polarization and Lorentzian effects. A semiempirical absorption correction from equivalent reflections was applied for all data sets according to Blessing's method.[24] The structures were solved by direct methods (SHELXL-97) and refined by full-matrix least-squares on F^2 (SHELXL-97).[24] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms at carbon were placed in calculated positions and refined isotropically using a riding model. For selected details of the crystallographic data see Table 1. CCDC-1003202 [(−)-(R_P)-7], CCDC-1003203 [(−)-(R_P)-**10**], and CCDC-1003204 [(+)-(S_P)-**14**] contain the supplementary data for these structures. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

Computational Details. The geometries of the investigated molecules were optimized on the DFT level using the TURBOMOLE 6.4 program package[25] and employing the TPSS[22] functional together with the D3(BJ)[23] dispersion correction and the def2-TZVP basis set.[21] The resolution-of-identity (RI) approximation for the Coulomb integrals[26] was applied using matching default auxiliary basis sets[27] and for the integration of the exchange-correlation contribution the numerical quadrature grid m4 was employed.

Single point calculations on the optimized geometries were performed with the global hybrid functional BHLYP[19] and the range-separated hybrid functional CAM-B3LYP[20] together with the def2-TZVP basis set[21] utilizing the development version of ORCA 3.0[28] (precursor of 3.0.1 release). The RI approximation for the Coulomb integrals was used in combination with the chain-of-spheres (COSX) approximation.[29] Rotatory strengths values for the electronic transitions from ground to singly excited states were obtained at the sTD-DFT level,[18] and all excitations up to a threshold of 10 eV were included. The molecular circular dichroism ($\Delta\varepsilon$) values were calculated by convoluting Gaussian functions with a width of σ = 0.4 eV which are centered at the wavelength of the electronic transitions and multiplied by the corresponding rotatory strength (vertical transitions). For all spectra the origin independent velocity representation of the rotatory strength was used.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of new compounds, chromatograms, theoretical simulation of CD spectra including the rotatory strengths for CAM-B3LYP, Cartesian coordinates of optimized structures, and CIF files containing the crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: arne.luetzen@uni-bonn.de.

Notes

The authors declare no competing financial interest.

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